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Research article

Quantitative volume-based morphometry in focal cortical dysplasia: A pilot study for lesion localization at the individual level

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ABSTRACT

Purpose: Surgical resection is the most effective treatment for focal cortical dysplasia (FCD). However, many patients with FCD have unremarkable or even negative findings on conventional magnetic resonance imaging (MRI). In this study, we explored the brain volume abnormalities of FCD patients at the individual level using an experimental volume-based morphometry algorithm and further estimated whether the volume abnormalities can help in the detection of FCD lesions.

Materials and methods: Sixteen patients with histologically-proven FCD lesions were retrospectively studied. Among them, eight patients had no visible abnormalities on routine MRI, three had abnormalities which partly matched the location of the surgical resection regions, and two did not match. For each patient, cerebral high-resolution T1-weighted magnetization-prepared rapid acquisition with gradient echo (MPRAGE) images were segmented into 45 structures, according to a brain anatomy template, and the volume of each structure was compared with an age- and gender-matched normal population at the individual level, based on a MorphoBox prototype. A Receiver Operating Characteristics (ROC) curve was used to evaluate the performance of the prototype in patients. To find the most appropriate threshold value for localizing the epileptogenic zones, deviations from the normative ranges of each resulting volume estimate were assessed by z-scores.

Results: Volume abnormalities including atrophic and hypertrophic volumes could be found in all the patients. Epileptogenic zones were found in brain structures with an abnormal volume in 87.5% (14/16) of patients. In 71.4% of patients (10/14), these zones were fully located in regions with an atrophic volume. This suggests that FCD lesions are more likely to be in regions with an atrophic volume than in those with a hypertrophic volume. When the best cut-off z-score value was –3.0, the sensitivity, specificity, and ROC area under the curve of the volume estimates were 93.9%, 79.6%, and 0.89, respectively.

Conclusion: Volume abnormalities can assist in the diagnosis of epileptogenic zones at the individual level in FCD patients with negative or positive findings on conventional MR images. Atrophic regions are more likely than hypertrophic ones to represent epileptogenic zones. Volume-based morphometry based on a MorphoBox prototype has potential to assist a careful scrutiny by radiologists with target in atrophic regions in patients who are initially deemed to be MR-negative, further trying to increase the detection rate of FCD.

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1. Introduction

Surgical removal of the epileptogenic zone is the most effective treatment for focal cortical dysplasia (FCD) [1]. However, nearly 45% of epileptogenic zones are not evident on conventional MRI, and the prognosis of patients without identifiable lesions on pre-surgical MRI is worse than that of patients with identifiable findings [2]. Therefore, it is important to use novel methods to improve the preoperative diagnostic rate of FCD. At present, voxel-based morphometric analysis (VBM) is the most popular advanced MR technology to improve the capacity for lesion detection at the individual level [3]. It highlights the typical features of FCD such as the blurring of the gray-white matter junction and the abnormal extension of gray matter [4,5]. Specifically, this method is focused on improving the visualization of lesions.

Apart from this focus, brain volume abnormalities (atrophy or hypertrophy) may also play an important role in FCD. One study at the group level reported that the surgical outcome of temporal lobectomy in patients with temporal lobe epilepsy was negatively correlated with the degree of frontal lobe atrophy [6]. Therefore, finding a quantitative method to evaluate volume abnormalities in FCD patients at the individual level has practical significance. Automated volumetric analysis is a worthwhile option because it is faster and easier to use, as well as more replicable than manual volumetric analysis. This kind of technique has already been used in hippocampal sclerosis [7–10]. However, to our knowledge, no automated volumetric analysis study has focused on FCD.

In this study, we retrospectively explored the brain volume abnormalities of FCD patients at the individual level and further estimated whether the volume abnormalities could help in the detection of FCD lesions, using a prototype volume-based morphometry algorithm called MorphoBox [11], which has been successfully used in vascular parkinsonism [12] and multiple sclerosis [13]. Compared to whole-brain VBM, MorphoBox provides volumes of specific structures of interest (such as the hippocampus or a lobe) and compares them to an age- and gender-matched normal population in an automated way. Because it focuses on an entire region of interest that comprises numerous voxels, the prototype is based upon the assumption that the overall effect of each voxel's abnormalities can become more obvious than when each single voxel is considered individually, which may increase the sensitivity to brain volume abnormalities. In addition, MorphoBox focuses on both the gray and white matter. Because FCD lesions are not usually restricted to one tissue class [14], combining the structural abnormalities of both the gray and white matter may lead to a better detection rate.

2. Material and methods

Sixteen patients (seven males; age, 26.4 ± 6.2 years) retrospectively enrolled from a consecutive series of patients who underwent resective surgery for intractable epilepsy between October 2014 and September 2015 at our hospital. The inclusion criteria included: (1) patients with a pre-surgical 3T MR exam with routine MR and high-resolution 3D T1-weighted magnetization-prepared rapid acquisition with gradient echo (MPRAGE) sequences; and (2) patients with histologically confirmed FCD (according to the Blümcke classification [15]). The exclusion criteria included: (1) patients with other brain diseases confirmed by routine MRI, or with any kind of mental illness, (2) patients younger than 19 years of age (due to the lack of age-matched healthy controls in our database); and (3) MPRAGE data that did not pass the image quality check [11,16]. This study was approved by the Ethics Committee of our hospital (Xuanwu Hhospital, Capital Medical University, Beijing, China). Written informed consent was obtained from all the study participants.

Each patient underwent a pre-surgical MR exam on a MAGNETOM Trio Tim 3 T MR scanner (Siemens Healthcare, Erlangen, Germany) using routine 2D (axial T1, T2, FLAIR, DWI, and coronal FLAIR) and high-resolution 3D T1-weighted MPRAGE sequences (sagittal, TR = 1800 ms; TE = 2.13 ms; TI = 1100 ms; flip angle = 9°; matrix size = 192 × 256 × 256; and voxel size = 1 mm × 1 mm × 1 mm). To find FCD lesions and eliminate any other obvious abnormalities and to obtain a “clinically determined gold standard” for the MR interpretation, all the images were reviewed by two radiologists (with ten and thirteen years' experience, respectively) and two neurosurgeons (with fifteen and twelve years' experience, respectively). These four examiners reviewed the images together. They were aware of all multimodality examinations, including clinical symptoms, EEG, and/or magneto-encephalography, intracranial EEG, SPECT, and/or PET-CT, the final surgical resection area, and each patient's individual pathology type. Differences in assessments among the reviewers were resolved by consensus. Patients with no abnormal findings on conventional MR images were defined as MR negative (MR–). Patients with abnormal findings on conventional MR images were defined as MR positive (MR +), no matter whether or not the positive findings were consistent with the location of the resection region.

The surgical resection regions (that were initially inferred by a previous preoperative multidisciplinary discussion and further confirmed by intra-operative electrocorticography and the pathologic diagnosis) were designated as the epileptogenic zones. Fourteen patients had at least one postoperative follow-up visit at one year, and the other two were lost to follow-up. The Engel Epilepsy Surgery Outcome Scale [17] was used to evaluate the effect of surgery.

Volume-based morphometry analysis was processed using the MorphoBox prototype. Detailed information regarding the MorphoBox and its specific working process has been previously reported [11]. Briefly, based on the 3D T1-MPRAGE images, the whole brain was segmented into 45 structures according to the brain's anatomy, and the absolute volume of each structure was estimated. These structures included global gray matter, white matter and CSF, the ventricular system (left, right, third, and fourth), cingulate gyrus, mesencephalon, pons, medulla oblongata, corpus callosum, bilateral thalamus/putamen/caudate/pallidum/deep white matter/hippocampus/insula/ cerebellum, and gray and white matter in the bilateral frontal/parietal/occipital/temporal lobes. For the inter-subject comparison, all the estimated volumes were normalized by the intracranial volume (TIV), resulting in volumes referred to as V. Deviations from normative ranges of resulting volume estimates were assessed by z-scores. Normative ranges were calibrated on healthy volumes estimated by MorphoBox from the 306 MPRAGE 3 T ADNI protocol [18] (http://adni.loni.usc.edu/methods/documents/mri-protocols/) using a log-linear regression model, taking into account the confounding effects of age and sex as covariates. A Receiver Operating Characteristics (ROC) curve (SPSS18, SPSS Inc., Chicago, IL, USA) was used to evaluate the performance of MorphoBox to localize the epileptogenic zones. The z-score at the best cut-off point was also obtained to find the most appropriate threshold value for localizing the epileptogenic zones.

When interpreting the findings of the MorphoBox prototype, certain factors are notable. Because it reflects the quantitative volume abnormalities of the 45 brain structures, the MorphoBox prototype displays the structure in which the lesion is located (such as the white matter in the left frontal lobe) rather than the exact coordinates of the lesion.

3. Results

Half of the 16 patients were found to be MR + as determined by the clinical group by consensus. The clinical profiles of the patients and their morphometric MRI analysis results are shown in Table 1, and detailed information is included in Table S1. Normative ranges were estimated using MorphoBox (age, 66.4 ± 19 years; age range, 19–90 years; 49% healthy female subjects; average number of subjects per half-decade, 30.6 ± 39). All the patients had brain structures out of the reference range from the healthy population. Specifically, 14/16